

Cyclodehydration of Acylated  $\alpha$ -Amino Acid Amides

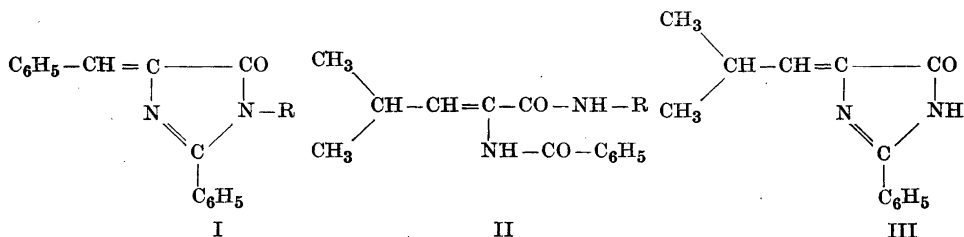
## II. Unsaturated Amides

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The preceding paper described the cyclisation of various tertiary  $\alpha$ -acylamido acid amides to saturated 5-imidazolones and reviewed briefly the relevant literature on former applications of the reaction to unsaturated  $\alpha$ -acylamido amides. The present communication is concerned with attempts to extend the scope of the reaction within the latter group.

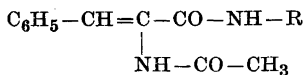
While the cyclisation of  $\alpha$ -benzamidoacrylamides to 4-benzylidene-5-imidazolones (I) is a well-established reaction, no case seems to be on record of an unsaturated, *aliphatic* amide being exposed to the usual ring-closure conditions. We have found that  $\alpha$ -benzamido- $\beta$ -isopropylacrylamide (II, R = H), easily prepared by ammonolysis of the unsaturated oxazolone, can be smoothly converted into 2-phenyl-4-isobutylidene-5-imidazolone (III) in alkali. Contrary to expectations, however, neither alkali-treatment, nor heating *in vacuo* above the melting point, resulted in cyclisation of the corresponding methylamide (II, R = CH<sub>3</sub>), which could be recovered in high yield



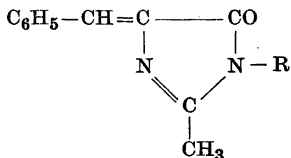
after the latter treatment. For comparison, the analogous N-methylcinnamamide was tested under similar conditions and found to yield the imidazolone (I, R = CH<sub>3</sub>) upon melting *in vacuo*. Treatment with aqueous alkali, however, resulted in hydrolysis of the amide-grouping without detectable ring-formation.

Attention was next directed to unsaturated amides carrying an aliphatic acyl-grouping. 2-Methyl-4-benzylidene-5-oxazolone was ammonolysed to  $\alpha$ -acetamidocinnamamide (IV, R = H) which could be smoothly converted

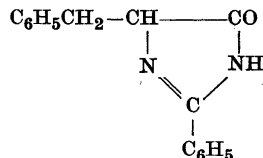
into 2-methyl-4-benzylidene-5-imidazolone (V, R = H) upon treatment with aqueous alkali. It was previously reported<sup>1</sup> that the analogous methylamide (IV, R = CH<sub>3</sub>) cyclised on heating to give the imidazolone (V, R = CH<sub>3</sub>).



IV



V

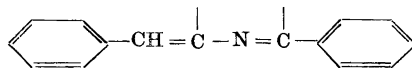


VI

The unsaturated imidazolones appear as high-melting crystalline compounds with yellow colours of varying intensity. Those having no substituent on the nitrogen-atom readily dissolve in alkali while all are only sparingly soluble in acid. The protolytic nature of the compounds were reflected in their UV-absorption spectra discussed below.

The easy preparative access of numerous unsaturated imidazolones by the Erlenmeyer-synthesis suggested a useful route to 4-substituted, saturated imidazolones by hydrogenation of the *exocyclic* double bond of the former. Some explorative experiments proved this to be a feasible preparative method. For example, when 2-phenyl-4-benzylidene-5-imidazolone in ethanol was shaken with a palladium catalyst and hydrogen, the theoretical amount of hydrogen was rapidly consumed with simultaneous disappearance of the yellow colour. The filtrate afforded a good yield of 2-phenyl-4-benzyl-5-imidazolone (VI). This result is in marked contrast to that of Gränacher and Mahler<sup>1</sup>. They found that catalytic hydrogenation of unsaturated imidazolones resulted in complete reduction, including the C = N-grouping of the ring. Our attempts to hydrogenate the unsaturated imidazolone exhaustively, resulted in a very slow uptake of the second molecule of hydrogen, followed by isolation of a mixture of partially and completely hydrogenated material. The latter was conveniently prepared by reduction with sodium amalgam as previously described<sup>1,3</sup>.

The ultraviolet absorption curves of the unsaturated imidazolones differ markedly from those reproduced in the preceding paper, belonging to compounds with no *exocyclic* double-bond. Ekeley and Ronzio<sup>2</sup> previously reported absorption data in dioxane and aqueous alkali for a product, formed upon reaction between benzamidine, glyoxal and benzaldehyde in alkaline solution. The spectra of this compound, later proved to be 2-phenyl-4-benzylidene-5-imidazolone<sup>3</sup>, are qualitatively similar to those reported in Fig. 1. There is a striking similarity between this spectrum and that of 2-phenyl-4-benzylidene-5-oxazolone<sup>4</sup>, suggesting that the main absorption is due to the same chromophoric system, *viz.*



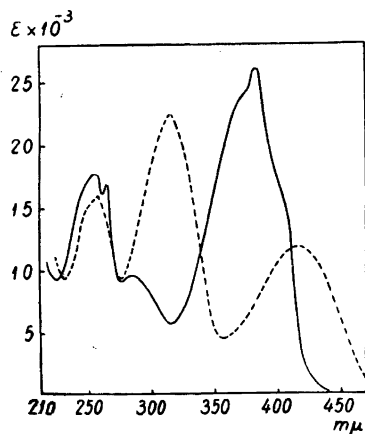


Fig. 1. Ultra-violet absorption spectrum of 2-phenyl-4-benzylidene-5-imidazolone in 96% ethanol: — and in 0.04 N ethanolic KOH: - - -.

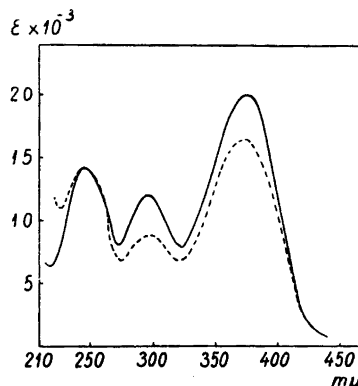
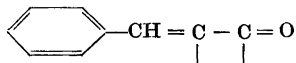


Fig. 2. Ultra-violet absorption spectrum of 1-methyl-2-phenyl-4-benzylidene-5-imidazolone in 96% ethanol: — and in 0.04 N ethanolic KOH: - - -.

In Fig. 2 the absorption spectrum of the N-methylated imidazolone (I, R = CH<sub>3</sub>) is shown. Although its general shape is unaltered, several small peaks and shoulders have disappeared; noteworthy is furthermore the minor influence of alkylation in this case, clearly demonstrating the acidic character of the imide-hydrogen of (I, R = H).

$\alpha$ -Benzamido- and  $\alpha$ -acetamidocinnamamide (IV, R = H) have similar absorption curves in methanol\* (Fig. 3), indicating the principal influence of the common grouping



on the resonating system involved in the absorption of light. In the imidazolone-series the exchange of a methyl substituent with a phenyl-group has a pronounced effect on the absorption curves.

UV-absorption spectra have further been provided for  $\alpha$ -benzamido- $\beta$ -isopropylacrylamide (II, R = H) and the corresponding imidazolone (Fig. 4). The former represents the characteristic benzamide-absorption, unchanged on addition of acid or alkali. The ring-closed product, however, has absorption data reminiscent of those of the benzylidene-compound (*cf.* Fig. 1); again, addition of alkali changes the spectrum profoundly.

When a freshly prepared solution of  $\alpha$ -acetamidocinnamamide in 0.01 N methanolic potassium hydroxide is kept at room temperature the imidazolone-formation can be followed spectrophotometrically (Fig. 5). The final curve agrees well with that obtained from the authentic imidazolone under similar

\* The spectra of  $\alpha$ -benzamidocinnamic acid and its hydrazone have been previously reported<sup>4,5</sup>. They differ only slightly from the curve of the corresponding amide shown in Fig. 3.

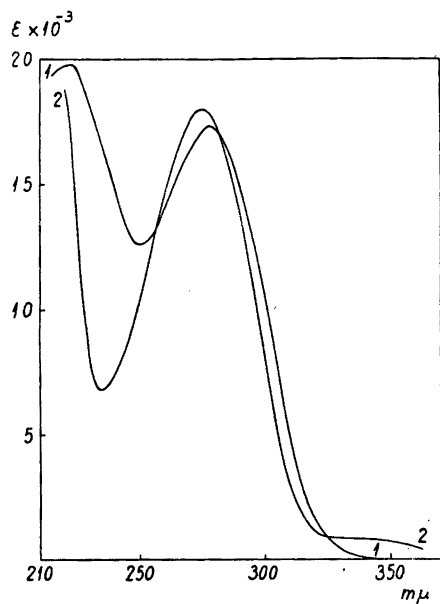


Fig. 3. Ultra-violet absorption spectra of 1:  $\alpha$ -benzamidocinnamamide and 2:  $\alpha$ -acetamidocinnamamide, both in methanol solution.

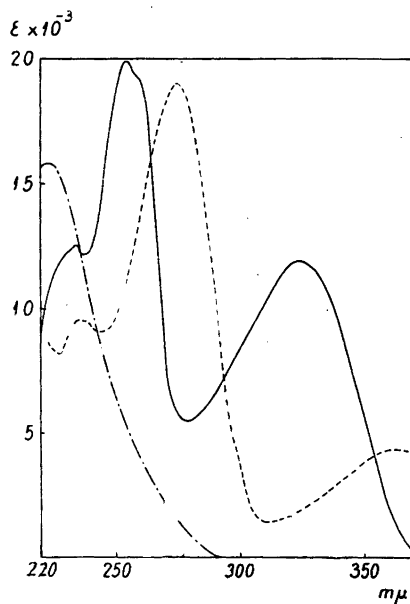


Fig. 4. Ultra-violet absorption spectra of  $\alpha$ -benzamido- $\beta$ -isopropylacrylamide in 96% ethanol: — and of 2-phenyl-4-isobutylidene-5-imidazolone in 96% ethanol: - - -. The curve: . . . represents the latter dissolved in 0.05 N ethanolic KOH.

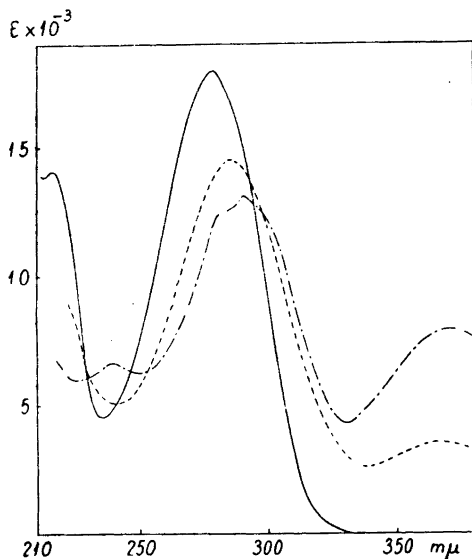


Fig. 5. Ultra-violet absorption spectra of a 0.08 M solution of  $\alpha$ -acetamidocinnamamide in 0.01 N methanolic KOH, measured immediately, and after standing at 23°. Immediately after dissolution: —; after 4 hours: - - - and after 21 hours: . . .

conditions. The rate of cyclisation in the present case is considerably higher than that reported in the preceding paper for analogous saturated amides. While more than 100 hours were required to cyclise the most favorable cases of the latter, the ring-closure of the present amide is virtually complete within *ca.* 20 hours.

## EXPERIMENTAL \*

*α-Benzamido-β-isopropylacrylamide.* 2-Phenyl-4-isobutylidene-5-oxazolone<sup>6</sup> was dissolved in ethanolic ammonia and kept for 3 days at room temperature. After concentration *in vacuo* and addition of water the amide separated. It crystallised, as a monohydrate, in colourless, rhombic plates from aqueous ethanol. M.p. 79–81°.

$C_{13}H_{16}O_2N_2 + H_2O$ (250.3)	Calc.	C 62.37	H 7.25	N 11.19
	Found	» 62.22	» 7.38	» 11.19

*2-Phenyl-4-isobutylidene-5-imidazolone.* The amide was dissolved in 2 *N* NaOH at 40–50° and acidified with glacial acetic acid, when pink crystals separated. Recrystallisation from ethanol, with addition of a little charcoal, yielded the imidazolone as clusters of pale yellow needles. M.p. 182° (decomp.). The compound is soluble in dilute alkali with a strong blue fluorescence.

$C_{13}H_{14}ON_2$ (214.3)	Calc.	C 72.85	H 6.59	N 13.08
	Found	» 72.49	» 6.40	» 13.08

*α-Benzamido-β-isopropylacrylmethylamide.* This was prepared in 91 % yield from the  $\alpha$ -lactone and methylamine in aqueous dioxane. The amide separated from dilute ethanol in colourless, flat prisms, m.p. 197°.

$C_{14}H_{18}O_2N_2$ (246.3)	Calc.	C 68.26	H 7.37	N 11.38
	Found	» 68.64	» 7.22	» 11.12

The amide is insoluble in alkali, even on heating, and several attempts to cyclise the substance at higher temperature proved fruitless. The crystalline starting material, contaminated with varying amounts of a dark brown oil, was the only product noticed after the reaction.

*α-Benzamidocinnammethylamide.* The amide resulted in 94 % yield when 2-phenyl-4-benzylidene-5-oxazolone was treated with ethanolic methylamine on the steam bath. It separated in clusters of colourless needles from ethanol. M.p. 188–189°. The amide proved very difficultly combustible in microanalysis, and it was only after mixing with potassium dichromate that correct figures were obtained.

$C_{17}H_{18}O_2N_2$ (280.3)	Calc.	C 72.83	H 5.75	N 9.99
	Found	» 72.73	» 6.02	» 9.99

*1-Methyl-2-phenyl-4-benzylidene-5-imidazolone.* While the above amide is unaffected by aqueous alkali and acid, heating at 200° *in vacuo* for 1.5 hours transformed it into an amorphous mass, which readily crystallised upon trituration with ethanol. Two recrystallisations from ethanol afforded the imidazolone as pale yellow needles, m.p. 135°.

$C_{17}H_{14}ON_2$ (262.3)	Calc.	C 77.83	H 5.38	N 10.68
	Found	» 77.98	» 5.47	» 10.72

*α-Acetamidocinnamide.* When 2-methyl-4-benzylidene-5-oxazolone<sup>7</sup> was dissolved in ethanolic ammonia, the separation of the amide started within a few minutes. It could be recrystallised from methanol as colourless needles. M.p. 198–200° (decomp.).

$C_{11}H_{12}O_2N_2$ (204.2)	Calc.	C 64.71	H 5.93	N 13.73
	Found	» 64.60	» 5.79	» 13.84

After the present work had been concluded, Rothstein<sup>8</sup> described this amide with m.p. 205° (decomp.).

*2-Methyl-4-benzylidene-5-imidazolone.* The above amide was treated with alkali in the usual fashion, yielding the imidazolone which separated from aqueous ethanol in yellow needles, m.p. 169–172° (decomp.).

$C_{11}H_{10}ON_2$ (186.2)	Calc.	C 70.94	H 5.41	N 15.05
	Found	» 70.62	» 5.60	» 15.15

\* All melting points are uncorrected and determined in capillary tubes in an electrically heated block, those below 80° in a water-bath.

*2-Phenyl-4-benzyl-5-imidazolone.* A solution of 2-phenyl-4-benzylidene-5-imidazolone in ethanol was shaken with Adam's PdO-catalyst in a hydrogen atmosphere at 1 at pressure. Within 30 minutes the calculated amount of hydrogen was taken up, followed by a sudden decrease in hydrogen-consumption. Upon evaporation of the filtrate, crystalline material separated from which traces of yellow impurities were removed by washing with a little ether. The colourless, crystalline powder melted at 250° under destruction and proved to give correct analytical figures without further purification. On rapid heating the m.p. 165–167° was observed.

C <sub>16</sub> H <sub>14</sub> ON <sub>2</sub> (250.3)	Calc.	C 76.78	H 5.64	N 11.20
	Found	» 76.68	» 5.42	» 11.14

*2-Phenyl-4-benzyl-5-imidazolidone.* The preparation was accomplished as previously described<sup>1</sup> by reduction of the unsaturated imidazolone with sodium amalgam and acetic acid in ethanol solution. Our product, twice recrystallised from xylene, melted sharply at 137–138°. Previously, the melting points 145–146° (Ref.<sup>1</sup>) and 150–151° (Ref.<sup>3</sup>) have been reported.

C <sub>16</sub> H <sub>16</sub> ON <sub>2</sub> (252.3)	Calc.	C 76.17	H 6.39	N 11.11
	Found	» 76.00	» 6.31	» 10.87

*Ultraviolet absorption spectra.* The UV-spectra were determined in 1 cm cells with a model DU Beckman quartz spectrophotometer.

#### SUMMARY

The cyclisation of unsaturated, aliphatic  $\alpha$ -benzamido acid amides and  $\alpha$ -acetamidocinnamamides to imidazolones is described.

The catalytic hydrogenation of the *exocyclic* double bond in unsaturated imidazolones has been demonstrated to occur. A new route to 4-substituted 5-imidazolones is suggested through this finding.

The characteristic UV-absorption spectra are presented and discussed.

Microanalyses were carried out in this laboratory by Mr. A. Grossmann.

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